DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

MINUTES OF A MEETING
April 30, 2004

Meeting Type: Public Feedback Meeting

Docket No.: 77N-0094 / CP16

Subject: Bayer HealthCare
Citizen's Petition
Proposed Amendment to the Final Rule for Aspirin Professional Labeling:
Primary Prevention of Myocardial Infarction

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Other Attendees:
Colin Baigent, BMBCh, M.Sc., Reader in Clinical Epidemiology
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Background
On November 19, 2003, the FDA held a public feedback meeting to discuss the issues raised during the review of Bayer's Citizen Petition submitted February 12, 2003. Specifically, the Petition requests the FDA to amend the final rule for professional labeling for aspirin to include the use of 75 mg and 325 mg aspirin for primary prevention of myocardial infarction in those individuals at significant risk. The following studies were provided for review in the Citizen's Petition:

- Physician's Health Study, 1988;
- British Doctor's Trial, 1998;
- Thrombosis Prevention Trial, 1998;
- Hypertensive Optimal Treatment Study (HOT), 1988;
- The Primary Prevention Project, 2001.

The material submitted in this Citizen's Petition was the topic of discussion during the Cardio-Renal Advisory Committee on December 8, 2003.

At the request of Bayer HealthCare, a second public feedback meeting was held on April 30, 2004 to continue the dialog between the FDA and Bayer.

Discussion

Following the opening comments of the meeting, Bayer made the following points:

- Bayer HealthCare reiterated that they were pursuing label expansion in order to clarify the appropriate use of aspirin, and wished to find common ground with the FDA. Further, Bayer believed that the data provided in the Citizen's Petition supports expanded labeling for aspirin as being effective as primary prevention for reducing risk of MI.

- Bayer felt the principle question is how to best communicate which population would benefit from aspirin therapy, and how to describe this through labeling. Bayer believes this is an evolutionary process, requiring ongoing dialog with the FDA. Further, while they agree that standards for safety and efficacy should not be waived, they believe that aspirin is underutilized.

Dr. Temple said that he felt there were two questions that needed to be answered, questions that were raised at the Advisory Committee. The first question is whether aspirin does in fact reduce the incidence of a clinically-meaningful outcome in subjects who have not yet had a myocardial infarction. The second question is the one raised by the sponsor: if there is such an effect, what population should aspirin be used in to prevent that clinical outcome and how should that be communicated.

FDA provided responses to questions submitted in the meeting background package. (See attached slides).

After discussing the responses to the questions, FDA requested that Bayer submit additional information to support their petition.

Additional Comments/Requests:

- The Agency believes that additional information from the TPT trial, including the primary data if available, would help describe the benefits of aspirin in the moderate-risk population.

- It was noted that approximately 27 countries currently allow the use of aspirin for primary prevention. FDA requested Bayer HealthCare to provide the aspirin labeling from those countries.

- In the December 8, 2003 Advisory Committee transcript (p. 236), Dr. Gaziano indicated that 80% of the MIs were confirmed. Please explain what this means. [Note: Dr. Gaziano was a consultant to Bayer at the Advisory Committee.]

- FDA requested that Bayer explain why the effects of aspirin on stroke and death

seen in the secondary prevention setting were not seen in the primary prevention trials. Dr. Baigen will provide the response.

- FDA requested that Bayer to provide comment on the relative risk/benefit of the 80 to 325 mg dose. During the Advisory Committee meeting, Dr. Topol provided information that suggested 80 mg was safer than 325 mg. If efficacy data indicates that 80 mg is efficacious and is safer than 325 mg, why should 325 mg be included in labeling?

- Bayer should provide a summary and description of other aspirin studies that are currently ongoing in the world.

- Bayer was asked to provide information on the use of serum markers in identifying an at risk population.

- Bayer should provide Dr. Baigen's analysis that classified subjects from the five studies into cardiovascular risk categories and analyzed endpoints based on this categorization. Please explain how the categorization was completed.

Conclusions

At the conclusion of the meeting, the floor was opened for other discussions and specific questions. None were raised. The meeting was then closed.

Attachment: Meeting Slides

Public Feedback Meeting with Bayer HealthCare

Aspirin Primary Prevention Citizen Petition
April 30, 2004
3:00 – 4:30 PM

Meeting Request

- Bayer requested this meeting to continue the dialogue regarding the safety and efficacy of aspirin for the primary prevention of myocardial infarction.
- Bayer provided 10 questions for FDA's consideration.

Question 1

- Many patients are at risk of MI in spite of not having a previous event. Does the Agency agree that such patients could be at as high a risk as those currently approved for secondary prevention?
- FDA RESPONSE: There is likely to be a population of people, without previous cardiac disease, who are at as high a risk as those currently approved for secondary prevention. These people could derive the greatest benefit from aspirin therapy, potentially supporting the use of aspirin in primary prevention in this subpopulation. The difficulty lies in identifying this subpopulation *a priori* and determining at what level the benefit outweighs the risk associated with chronic aspirin use. Given the risks associated with the use of aspirin, it is important to understand the risk and benefit for subgroups in a population.

Question 2a

- Data from five Primary Prevention trials involving over 55,000 patients were presented in support of the proposed labeling for the use of aspirin in patients at moderate risk of MI. One of these studies in particular, TPT, included patients in the population of interest. While the other four studies were obviously of lower risk, they support the effectiveness of aspirin in "at risk" patients.
- How can the database be used to support efficacy in moderate risk patients?

Response to Question 2a

- The data from these trials provide important information on the effectiveness of aspirin in a low risk population. The TPT trial may be helpful in further defining the benefit in a moderate risk population but would require Agency review of the protocol and primary data.
- Areas that need further consideration are benefit and risk of different subgroups (*e.g.* high blood pressure, women).
- In assessing the efficacy information, it is important to look at absolute risk reduction rather than relative risk reduction alone. This also pertains to the presentation of the information related to absolute risk increase for adverse events. This will allow for a more informed assessment of benefit/risk.

Question 2b

- As a point of reference, the approved use of aspirin for prevention is stable angina patients is based on a single study (SAPAT). While the benefits observed in these studies are restricted to non-fatal MI, this represents an important and meaningful finding.
- Does the FDA agree that a product that significantly reduces the most common form of MI should be so labeled?
- FDA RESPONSE: If it is to be labeled, this appears to be the only claim that could be considered. Unlike the data supporting some of the secondary prevention claims for aspirin, there is no suggestion that other cardiovascular endpoints do not appear to be improved significantly by aspirin in the low risk primary prevention population.

Question 2c

- Because of the difficulties in classifying the silent MI, these events are usually excluded from study designs. We are curious as to why the Agency placed so much emphasis on this endpoint (including the re-evaluation of studies to include the endpoint when not prospectively defined)?

- FDA RESPONSE:
  - We do not agree it is difficult in classifying silent MI. Their clinical importance seems difficult to refute; regardless of whether some studies elected not to collect information on their occurrence.
  - Data collected on silent MIs in clinical trials should not be ignored simply because it may not yield the expected results and should be included in analyses whenever available.

Question 3a

- Does FDA consider the number of female subjects studied sufficient to include women in the labeling, given that there were significantly more women in these trials combined than the number of female subjects the Agency currently reviews as part of NDA approvals?

- FDA RESPONSE:
  - Many members of the advisory committee expressed concerns about the data in women.
  - The data in women from these trials are not supportive of a significant effect in the population studied.

Question 3b

- If not, is FDA aware of any evidence to suggest women would differ from men with respect to aspirins effects?
  - There was a 10-year gap between the approval of aspirin use for recurrent stroke in men and women. The ten years between the 1988 Tentative Final Rule which excluded women and the 1998 Final Rule ultimately recognized that there were no gender differences in aspirin's benefit.
- FDA RESPONSE
  - It will be important for FDA to understand how you interpret the differential effect in women as compared to men in the clinical trials and what basis you use to dismiss it.
  - As noted by members of the advisory committee, there are differences in the results of the secondary prevention data and primary prevention data with regard to benefit and treatment effect.

Preamble to Question 4

- Major professional medical organizations including the American Heart Association, the American Diabetes Association and the United States Preventative Services Task Force support the Petition and have published guidelines for practicing physicians and recommend aspirin for primary prevention in those patients at sufficient risk suggesting that physicians can adequately assess risk. These organizations recognize the benefits/risk based on thorough review of the data and have determined the significant public health impact of broader appropriate use of aspirin.

Question 4

- Does FDA agree with the position of these bodies and if so, is FDA prepared to consider labeling similar to those suggested by these guidelines?
- FDA RESPONSE:
  - It is not the role of the FDA to agree or disagree with the recommendations of these groups. The FDA will look at the type of information used by these groups, their analyses, and interpretations as a part of our deliberations.
  - FDA reviews the available data and determines whether there is sufficient information for the effective and safe use for a population of subjects that would justify labeling.
  - FDA is not aware that a majority of physicians are able to assess risk in patients. If aspirin for secondary prevention is under prescribed, this does not support your suggestion that physicians understand risk assessment.

Question 5

- The Agency is clearly comfortable with risk based labeling as evidenced by current statin labeling.
- Is it the Agency's view that similar language could be constructed for aspirin?
- FDA REPSONSE:
  - Risk-based labeling is one approach that may be used if the product is to be labeled for primary prevention.
  - The statin labeling is based on prospective application of a scoring system. Such risk-based labeling is otherwise quite uncommon in drug labeling. A more common approach, one easily understood by physicians, is the application of selected demographics to identify patients at higher risk. The sponsor has not made a case that such an approach is unsuitable in this setting.

Question 5 (cont)

- FDA RESPONSE (cont):
  - Some AC members were concerned that blood pressure is a component of some of the risk scoring systems. It was noted that there seemed to be a differential effect based on blood pressure. The sponsor has not provided any justification for their selection of the risk scoring system.
  - Labeling may also provide additional information on drug therapy in subgroups (HTN, gender) that may not be covered by general risk scoring systems.
  - Has the sponsor considered using new serum markers of inflammation as a method to identify subgroups of higher risk?

Preamble to Question 6

- The briefing material presented to the Advisory Committee by FDA indicated that the FDA was not in possession of all of the original study protocols associated with the key trials described in the Citizen Petition.

Responses to Question 6

- If the protocols were available to the FDA, what questions might have been answered?
- FDA RESPONSE:
  - FDA uses the original protocol to evaluate for post-hoc reporting changes including:
    - Pre-specified endpoints
    - Pre-specified definitions of endpoints
    - Trial conduct
- Would the FDA like Bayer's assistance in helping obtain the protocols?
  - FDA RESPONSE: It would be helpful if the protocols and data were available for review.
  - As commented on below, additional data from the one trial conducted in moderate-risk populations, the TPT trial, is sought by the Agency.

Question 7

- Based on the substantial evidence in favor of broader use of aspirin (and actual use in clinical practice), additional studies in this area appear unwarranted and unethical.
- Does the FDA agree?
- FDA RESPONSES:
  - Several members of the advisory committee supported an additional study. Until FDA completes its review of the data, this option remains open.
  - Because a mortality benefit has not been demonstrated in the primary prevention population, another study may not be precluded based on ethical considerations. The ethics of conducting another study depends on a benefit risk assessment in the population studied.

Question 8

- There have been over 200 studies involving more than 150,000 patients that have looked at the long-term safety of aspirin. Bayer continues to believe that the large secondary prevention database, as well as, the 55,000 patients in 5 primary prevention trials provides meaningful insight regarding the intended use.
- Does the FDA agree that safety data from these studies is relevant to establishing the benefit to risk relationship for aspirin in moderate risk patients?

Response to Question 8

- Safety data from previous studies are relevant.
- In the material Bayer provided in the petition, and the material for the advisory committee, you provide point estimates of the prevalence of hemorrhagic strokes and gastrointestinal bleeding on the overall population in these studies. This alone is inadequate for FDA to make safety assessments in subpopulations that may have a greater risk of these events.
- Please provide additional information on the differential risk of hemorrhagic stroke, and gastrointestinal bleeding in various subpopulations.

Question 9

- Evidence was presented at the Advisory meeting highlighting the significant underutilization of aspirin in "at risk" patients (including those in currently approved indications).
- How can Bayer, in a partnership with the FDA and the medical community develop labeling to help address this unfortunate public health reality?

- FDA RESPONSE
  - Where did Bayer obtain information on utilization rates of aspirin in at risk populations?
  - Before embarking on a change in labeling, it is important to understand why "at risk" patients are not being placed on aspirin.

Question 10

- Can the FDA provide an update on the timing and process for completing the review of the petition?

- FDA RESPONSE:
  - The FDA is interested in obtaining additional details regarding the TPT trial, including the primary data if at all possible. Additional comment is also sought from the sponsor regarding the risks and benefits of ASA in relevant sub-populations, including women. Finally, an analysis of risk and benefit using a more usual metric of risk would help us determine the most appropriate means of determining who might benefit from ASA for primary prevention. Once these data requests are addressed sufficiently, the FDA aims to complete its review promptly.

- How can Bayer work with the Agency to help address the apparent discrepancies between the investigator analyses and the Agency medical review?

- FDA RESPONSE:
  - Bayer needs to be more specific as to what discrepancies they refer.

Additional Comment

- TPT Trial
  - The Agency believes that additional information regarding this trial, including the primary data if available, would help describe the benefits of ASA in the moderate-risk population proposed by the sponsor.
  - The paper reports a fairly high withdrawal rate from the study. It is unclear how the withdrawals were handled in the analysis. Were withdrawn subjects followed until the completion of the trial and included in the analysis up to completion even if they went off therapy?

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5-26-04

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 77N-0094/CP16

TO: Dockets Management Branch, HFA-305

☑ The attached material should be placed on public display under the above referenced Docket No.

☐ This material should be cross-referenced to Comment No. _____

Charles J. Ganley, M.D.

Attachment